IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: A.P. Wolffe *et al.* Application No.: 10/083,682 Filed: October 24, 2001 For: LIBRARIES OF REGULATORY SEQUENCES, METHODS OF MAKING AND USING SAME (as amended)	Examiner: S. Zhou Group Art Unit: 1631 Confirmation No.: 1541

REPLY TO EXAMINER'S ANSWER

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

In accordance with 37 C.F.R. § 41.41, Appellant submits one copy of this Reply Brief in response to the Examiner's Answer. The Examiner's Answer was mailed May 8, 2007, making a Reply Brief due by July 8, 2007. Accordingly, this Reply Brief is timely filed.

RELATED APPEALS AND INTERFERENCES

Appellant notes that a Decision on Appeal in parent application USSN 09/844,501 was mailed on December 21, 2006. The Board reversed all rejections and the parent application issued as U.S. Patent No. 7,217,509 on May 15, 2007. A copy of the Decision in the parent case is attached hereto in the Related Proceedings Appendix.

STATUS OF THE CLAIMS

Claims 66-71 and 125-128 as shown in the Claims Appendix are on appeal.

GROUND OF REJECTION

1. Claims 66-71 and 125-128 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by pages 177-183 of the Clontech Catalog (hereinafter "Clontech").

Appellant notes that the rejection of claims 66-71 and 125-128 under 35 U.S.C. § 112, 1st paragraph (written description) has been withdrawn in view of Appellant's arguments in their Appeal Brief. (See, Examiner's Answer, page 3).

ARGUMENTS

1. Anticipation Has Not Been Established

The rejection of all pending claims as allegedly anticipated by the Clontech catalog was reiterated in the Examiner's Answer on the grounds that the claimed libraries are product-by-process claims and the resulting product is not distinguishable from Clontech's genomic libraries (Examiner's Answer, pages 4-5). In support of the rejection, it was again maintained that the use of the transitional phrase "consisting essentially of" is (Examiner's Answer, page 5):

> interpreted that the claimed polynucleotide, i.e., the insert can includes sequence from accessible regions and sequence other than accessible region. Thus, the libraries disclosed by Clontech and certain clones contained therein are the same as the polynucleotides or library thereof in the instant product-by-process claims.

Applicants again note that even if "certain clones" in the Clontech library include sequences corresponding to accessible regions, this is insufficient to establish anticipation. Anticipation is a rigorous standard and in order to show inherent disclosure of the claimed libraries, it must be shown is that each and every insert in Clontech's libraries necessarily consists essentially of a sequence corresponding to an accessible region. For the reasons of record, Clontech's libraries, made from naked DNA, do not consist essentially of inserts as claimed, namely inserts made from cellular chromatin that correspond to accessible regions. In fact, Clontech's libraries differ from the claimed libraries by virtue of the process used to make them and, as such, the Examiner's assertions cannot be supported by any evidence and are untenable.

(a) The transition phrase "consisting essentially of" cannot be interpreted to encompass library inserts lacking sequences corresponding to accessible regions

The Examiner continues to assert that the use of the transitional phrase "consisting essentially of" renders the claimed libraries open to clones that include sequences corresponding to non-accessible regions. (Examiner's Answer, page 5). Appellants do not dispute that the claimed libraries might, on rare occasions, include inserts that, in addition to the accessible sequences include small amounts of sequence corresponding to inaccessible. However, because the claimed libraries are made from cleaving cellular chromatin (in which inaccessible regions are protected from cleavage by associated proteins), the inserts in the library of the claims will never include only inaccessible regions and, moreover if any sequences corresponding to inaccessible regions are present in these inserts, they will be immaterial.

In any event, the question is not whether the claims on appeal read on inserts including both sequences corresponding to inaccessible and accessible regions. The relevant question is whether the inserts of the claimed libraries include sequences corresponding only to inaccessible regions. For the reasons of record and reiterated herein, the use of the transitional phrase "consisting essentially of" means that claimed library must include inserts with sequences

corresponding to accessible regions. These inserts may also include sequences corresponding to inaccessible regions because these additional (non-accessible) sequences do not materially affect the accessible sequences of the insert. See, for example, MPEP 2111.03. Therefore, while sequences corresponding to inaccessible sequences can optionally be present in any insert of the claimed libraries, an insert that corresponds solely to inaccessible regions is excluded from the scope of the claims on appeal; as such inserts would materially affect the basic and novel characteristic of the claimed polynucleotides.

Consequently, because the libraries disclosed in the Clontech catalog will include inserts that do not "consist essentially of" sequences corresponding to accessible regions, this reference does not anticipate the claims on appeal.

(b) Clontech's libraries are distinguishable from the claimed libraries

As noted by the Examiner, the pending claims are drawn to libraries produced by specified process steps. However, contrary to the Examiner's continued assertions, the recited process steps generate libraries that are distinguishable from Clontech's libraries.

The claimed libraries are composed of fragments including accessible regions. As set forth in step (a) of claim 66, these fragments are made by cleaving cellular chromatin with a probe. Because cellular chromatin includes chromosomal proteins that protect non-accessible regions from digestion, this process step necessarily gives rise to fragments that consist essentially of accessible regions. Furthermore, step (d) of claim 66 requires that the cleaved fragments that are cloned into the vector to make the library include an end generated from the cleavage from cellular chromatin in step (a). As a result of these process steps, the claimed libraries consist essentially of accessible regions and are distinguishable from libraries made from naked DNA.

Indeed, as described in the specification and previously noted, cellular chromatin, with its associated proteins, is utterly distinguishable from naked DNA, which Clontech digests to make

their libraries.[1] There are no circumstances under which digestion and cloning of naked DNA (Clontech) could produce a library of polynucleotides consisting essentially of accessible regions, as claimed. Rather, digestion of naked DNA produces a collection of polynucleotides representative of the entire genome and, therefore, there will be inserts whose sequences correspond only inaccessible regions. Since inserts corresponding only to inaccessible regions are excluded from the pending claims, Clontech's libraries are necessarily distinguishable from the claimed libraries.

Simply put, Appellant has clearly demonstrated that the recited process steps, for example, cleaving of cellular chromatin with a probe and cloning fragments including one end cleaved by this probe, impart a patentable distinction between the claimed libraries (which must include inserts corresponding to accessible regions of cellular chromatin) and Clontech's libraries (which include inserts corresponding to inaccessible regions because they are made from naked DNA). Accordingly, the claimed libraries are distinguishable from the libraries marketed in the Clontech catalog.

Furthermore, as previously noted, the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic" of the reference. *Ex parte Skinner,* 2 USPQ2d 1788 (BPAI 1986), emphasis added. No such evidence or reasoning, but, instead, has merely asserted that the cited reference, disclosing a genomic library made from naked DNA and including inserts that do not "consist essentially of" sequences corresponding to accessible regions of cellular chromatin, inherently discloses the particularly claimed subject matter.

Thus, Clontech fails to describe, expressly or inherently, polynucleotides and libraries as claimed. Therefore, Appellant submits that the rejection cannot be sustained and should be withdrawn.

[1] See, *e.g.*, Responses dated December 8, 2004 and May 24, 2005

CONCLUSION

For the reasons stated above, Appellant that the pending claims are patentable over the art cited by the Examiner. Accordingly, Appellant requests that the rejection of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: July 5, 2007

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CLAIMS APPENDIX

66. A polynucleotide, wherein the polynucleotide is a member of a library of polynucleotides, the members of the library comprising a vector and an insert, wherein the insert sequences consist essentially of accessible regions of cellular chromatin, wherein the library is obtained according to the method of:

(a) contacting cellular chromatin with a probe, wherein reaction of the probe with cellular chromatin results in polynucleotide cleavage at accessible regions of cellular chromatin;

(b) deproteinizing the cleaved chromatin of step (a);

(c) digesting the deproteinized chromatin of step (b) with a nuclease to generate a collection of polynucleotide fragments; and

(d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage.

67. A library comprising a plurality of polynucleotides according to claim 66.

68. The library of claim 67, wherein the cellular chromatin is obtained from cells at a particular stage of development.

69. The library of claim 67, wherein the cellular chromatin is obtained from cells of a particular tissue.

70. The library of claim 67, wherein the cellular chromatin is obtained from diseased cells.

71. The library of claim 67, wherein the cellular chromatin is obtained from infected cells.

125. The polynucleotide of claim 66, wherein, in step (a), the probe is a nuclease.

126. The polynucleotide of claim 125, wherein the nuclease is a restriction enzyme.

127. The polynucleotide of claim 126, wherein the probe comprises a plurality of restriction enzymes.

128. The polynucleotide of claim 66, wherein, in step (c), the nuclease is a restriction enzyme.

EVIDENCE APPENDIX

No documents are submitted with the Evidence Appendix.

RELATED PROCEEDINGS APPENDIX

As noted above on page 2 of this Reply Brief, a Decision on Appeal in USSN 09/844,501 was mailed on December 21, 2006 reversing the Examiner. A copy of that Decision is attached hereto.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ALAN WOLFFE and FYODOR URNOV

Appeal No. 2006-2851
Application No. 09/844,501

ON BRIEF

Before ADAMS, MILLS, and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 123-152.

Claims 123 reads as follows:

123. A method for preparing a library of regulatory DNA sequences from a cell, the method comprising:
(a) providing a cell nucleus, wherein the nucleus comprises cellular chromatin;
(b) contacting the nucleus with a first enzyme, wherein the first enzyme reacts with accessible regions of cellular chromatin;
(c) deproteinizing the cellular chromatin to generate deproteinized DNA;

(d) contacting the deproteinized DNA with a second enzyme to generate DNA fragments;

(e) contacting the DNA fragments obtained in step (d) with a population of vector molecules, wherein the vector molecules comprise a first end that is compatible with the first enzyme and a second end that is compatible with the second enzyme, under conditions favorable to ligation of compatible ends; and

(f) selecting polynucleotides comprising a DNA fragment ligated to a vector molecule.

The prior art cited by the examiner is:

Li et al. (Li)	5,500,356	March 19, 1996
Grosveld et al. (Grosveld)	5,635,355	June 3, 1997
Chung	6,644,421	Sept. 3, 2002

NEB Catalog, pp. 32, 46, 48, and 83 (1995)

Grounds of Rejection

Claims 123-128, 130, 135, 143-145, and 147-151 stand rejected under 35 U.S.C. § 103(a) over Grosveld.

Claims 129, 131-133, and 152 stand rejected under 35 U.S.C. § 103(a) over Grosveld taken with Li.

Claims 136-142 stand rejected under 35 U.S.C. § 103(a) over Grosveld taken with NEB catalog (1995).

Claims 134 and 146 stand rejected under 35 U.S.C. § 103(a) over Grosveld taken with Chung.

We reverse these rejections.

DISCUSSION

35 U.S.C. § 103

Claims 123-128, 130, 135, 143-145, and 147-151 stand rejected under 35 U.S.C. § 103(a) over Grosveld.

According to the examiner Grosveld teaches each of the claimed steps, with particular reference to column 8, lines 1-25, column 15, lines 43-47 and column 21, lines 18-20 and claim 1 (Answer, pages 3-4).

Upon review of the disclosure of Grosveld, we do not find the examiner has provided sufficient evidence to support a prima facie case of obviousness of the method of claim 123.

We agree with the Examiner that Grosveld describes steps (a)-(d) of the method of claim 123 at Column 8, lines 1-25, we do not find that Grosveld describes a method consistent with steps (e)-(f) of the claimed method.

In particular, claim 123, step (e) recites, "contacting the DNA fragments obtained in step (d) with a population of vector molecules, wherein the vector molecules comprise a first end that is compatible with the first enzyme and a second end that is compatible with the second enzyme, under conditions favorable to ligation of compatible ends."

Grosveld at column 8, lines 16-32, describes deproteination steps and digestion with a second enzyme to generate fragments, such as BglII, consistent with steps (c)

and (d) of claim 123. Then, the "exact location of the DNaseI hypersensitive site[s] of the 3' of the adult β-globin gene were determined using two single copy DNA probes and several restriction enzyme digests of DNaseI digested HEL nuclei. The data summarized in FIG. 2 (A-D) show that there is a single DNaseI hypersensitive site between the 2.3 kb BglII fragment and the 2.4 kb HindIII fragment . . ." Column 8, lines 48-51. Accordingly, Grosveld obtained fragments of the adult β-globin gene and probed these fragments to locate the DNaseI hypersensitive site. Grosveld did not, according to claim 123, step (e), contact the DNA fragments obtained in step (d) with a population of vector molecules, wherein the vector molecules comprise a first end that is compatible with the first enzyme and a second end that is compatible with the second enzyme, under conditions favorable to ligation of compatible ends; or step (f), select polynucleotides comprising a DNA fragment ligated to a vector molecule. Grosveld, on the other hand, probed DNA fragments which were not ligated to a vector, and selected the DNA fragment of interest having the DNaseI hypersensitive site by its ability to bind to a probe.

In a different experiment, Grosveld incorporated the previously identified DNAse I hypersensitive sites into a vector or plasmid containing both the hypersensitive sites and the adult β-globin gene. Column 15, lines 6-47. The DNA fragments cloned in the experiment described in column 15 are not the same as the fragments described in column 8. In particular, the hypersensitive site (HSS)-containing fragments cloned in col. 15 are not the DNAse/I restriction enzyme fragments from col. 8. See col. 15, lines

45-46: PvuI-BstEII fragment with HSS 1 and 2; BstEII-ClaI fragment with HSS 3 and 4.

In contrast, appellants describe their method in the specification, pages 49-50, as follows.

> In another embodiment, cellular chromatin is subjected to limited nuclease action, and fragments having one end defined by nuclease cleavage are preferentially cloned. For example, isolated chromatin or permeabilized nuclei are exposed to low concentrations of DNase I, optionally for short periods of time (e.g., one minute) and/or at reduced temperature (e.g., lower than *37°C).* DNase-treated chromatin is then deproteinized and the resulting DNA is digested to completion with a restriction enzyme, preferably one having a four-nucleotide recognition sequence. ... Preferential cloning of nuclease-generated fragments is accomplished by a number of methods. For example, prior to restriction enzyme digestion, nuclease-generated ends can be rendered blunt-ended by appropriate nuclease and/or polymerase treatment (e.g., T4 DNA polymerase plus the 4 dNTPs). Following restriction digestion, fragments are cloned into a vector that has been cleaved to generate a blunt end and an end that is compatible with that produced by the restriction enzyme used to digest the nuclease treated chromatin. ... Ligation of adapter oligonucleotides, to nuclease-generated ends and/or restriction enzyme-generated ends, can also be used to assist in the preferential cloning of fragments containing a nuclease-generated end. For example, a library of accessible sequences is obtained by selective cloning of fragments having one blunt end (corresponding to a site of nuclease action in an accessible region) and one cohesive end ...

In the method of claim 123, it is only after the DNA fragments have been ligated to a vector molecule that the polynucleotide of interest is selected. See, Example 15, specification, page 114, lines 6-14, wherein E.coli colonies harboring insert-containing plasmids were identified and screened.

While both appellants and the examiner rely heavily on argument with respect to potential limitations within the preamble the claims, we do not find it necessary to reach

this issue to decide the case before us. For the reasons discussed herein, we do not find the examiner has provided sufficient evidence to support a prima facie case of obviousness. The rejection of the claims over Grosveld is reversed.

35 U.S.C. § 103(a)

Claims 129, 131-133 and 152 stand rejected under 35 U.S.C. § 103(a) over Grosveld taken with Li. Claims 136-142 stand rejected under 35 U.S.C. § 103(a) over Grosveld taken with NEB catalog (1995). Claims 134 and 146 stand rejected under 35 U.S.C. § 103(a) over Grosveld taken with Chung.

With respect to the other pending obviousness rejections before us, all rejections stand or fall on the relevance of Grosveld to the pending claims. The examiner relies on the NEB catalog to make up for a failure of Grosveld to teach specific restriction enzymes (Answer, page 6), Li for a failure of Grosveld to teach a comparison of cells from a variety of different sources (Answer, page 7), and Chung for the failure of Grosveld to teach embedding cells in agarose prior to enzymatic cleavage (Answer, page 9).

We do not find that either NEB catalog, Li or Chung overcome the above noted deficiency of Grosveld and its failure to teach steps (e) and (f) of claim 123, and therefore the rejections for obviousness over Grosveld taken with NEB catalog, Li or Chung are reversed.

CONCLUSION

The rejections of the claims under 35 U.S.C. § 103(a) over Grosveld alone or in view of NEB, Li or Chung are reversed.

REVERSED

Donald E. Adams
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

Eric Grimes
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

Appeal No. 2006-2851
Application No. 09/844,501

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PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on **July 5, 2007**

7/5/07 Michelle Hobson

Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: S. Zhou
WOLFFE et al.	Group Art Unit: 1631
Serial No.: 10/083,682	Confirmation No.: 1541
Filing Date: October 24, 2001	Customer No.: 20855
Title: LIBRARIES OF REGULATORY SEQUENCES; METHODS OF MAKING AND USING SAME (as amended)	

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

x Reply to Examiner's Answer (6 pages) with attached Claims Appendix (2 pages), Evidence Appendix (1 page) and Related Proceedings Appendix (1 page) with copy of the Decision on Appeal from USSN 09/844,501 (8 pages)

x Return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	10	- 124	0	x $50.00	$0
Independent Claims	1	- 23	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Appeal Brief Fee					$0
Small Entity Reduction (if applicable)					$0
TOTAL FEE DUE					$0

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: July 5, 2007

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